

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No. : 10/598,691  
Confirmation No. : 9035  
Applicant(s) : Philip Wilson Howard et al.

Electronically filed by Tracy Bruck Kifle on 12/1/08

Filing Date : February 14, 2007  
Title : PYRROLOBENZODIAZEPINES

TC/A.U. : 1624  
Examiner : Bruck Kifle

Docket No. : 065435-9082-US00

Customer No. : 023510

**DECLARATION OF PHILIP WILSON HOWARD**  
**UNDER 37 C.F.R. §1.132**

Mail Stop Amendment  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

I, Philip Wilson Howard declare as follows:

1. I have personal knowledge of the following facts and I make this declaration in support of the prosecution of U.S. Patent Application Serial No. 10/598,691 ("the Application") before the United States Patent and Trademark Office.

2. I am currently a consultant to SpiroGen Limited, a position I have held since September 2008. Prior to that I was Director of Chemistry of SpiroGen Limited and a Senior Research Fellow of the School of Pharmacy, University of London. My *curriculum vitae* is attached as Exhibit A.

3. I am a co-inventor of the subject matter of the above-referenced Application.

4. I understand that in an Office action dated September 29, 2008, Examiner Kifle finally rejected claims 1, 3-5, 7, 10 and 14-16 of the Application under 35 U.S.C. §103(a) as being obvious over PCT Publication No. WO 93/18045 ("Thurston et al.").

Thurston et al. is cited by the Examiner for teaching a generic group of pyrrolobenzodiazepine derivatives.

5. The compound claimed has better properties than those disclosed in Thurston et al. that would not be predicted by one of ordinary skill in the art. For example, as disclosed in the specification of the Application at page 41, the claimed compound has an  $IC_{50}$  value in an assay using K562 human chronic myeloid leukaemia cells of about 0.05 nanomolar. This  $IC_{50}$  value is superior and unexpected from the teachings of Thurston et al., which discloses an  $IC_{50}$  value in an assay using K562 cells of 10 nM for a compound in which the group linking the pyrrolobenzodiazepine moieties contains three carbons (example 6) compared to the five carbon linking group of the claimed compounds and an  $IC_{50}$  value of 0.5 micromolar for a compound (example 4) that differs from the claimed compound by having no substituents on the PBD C-ring.

6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1/12/2008  
\_\_\_\_\_  
Date

  
\_\_\_\_\_  
Philip Wilson Howard

Attachment: Exhibit A

## **Dr Philip W. Howard**

24/6/1964

British

Male

Director of Chemistry, Spirogen

E-mail1: [philip.howard@pharmacy.ac.uk](mailto:philip.howard@pharmacy.ac.uk)

E-mail2: [philip.howard@spirogen.com](mailto:philip.howard@spirogen.com)

Address: 3 Westbourne Mews, St Albans, AL1 1LS, Herts

Tel. (Home): 01727 850257

Tel (Work, Direct Line): 0207 7535934

Mob: 077 6202 2522

---

### **Qualifications**

PhD University of East Anglia, "The Preparation and Chemistry of Dihydrocatechol Derived Organoiron Complexes".

BSc (2.1) Applied Chemistry, Kingston Polytechnic

---

### **Key Achievements**

- Proven track record in anticancer drug discovery
  - SJG-136 (SG2000) phase I/II clinical candidate
  - SG2285 a promising preclinical candidate
  - 14 Years experience of leading chemists
  - 50 Peer Reviewed scientific papers (See Appendix)
  - 17 Patents
- 

### **Career**

**September 2008** – Chemistry and IP Consultant to Spirogen

**2001- September 2008:** Director of Chemistry Spirogen /Senior

Research Fellow, University of London, School of Pharmacy.

**1999-2001:** Senior Research Fellow, University of Nottingham

**1995-1999:** Senior Research Lecturer, University of Portsmouth

**1993-1995:** Post Doctoral Fellow, University of Portsmouth

**1990-1993:** Post Doctoral Fellow, SmithKline Beecham

---

## General Skills

- Design, synthesis and optimization of novel anticancer agents
  - Leading and supervising chemists (Spirogen chemistry team members, post docs, PhD, MSc and undergraduate students)
  - Managing synthetic drug discovery projects
  - Liaising with in-house biologists and interpreting biological and analytical data
  - Collaborating with external research partners
  - Running and organizing an 18-chemist laboratory (COSHH etc)
  - Writing scientific reports, papers and drafting patents
  - Presenting scientific results (at internal meetings, invited lectures at scientific conferences, and open days to members of the public)
  - Preparing "Due Diligence" and presenting research at VC meetings
  - Organizing scientific workshops for Spirogen staff and post graduates
  - Chemistry related computer software packages Activity Base, Chemdraw, Scifinder Scholar etc.
  - Designing two chemistry laboratories (layout, number of hoods, services etc)
- 

## Technical Chemical Skills

- Working with moisture and air sensitive reagents (standard syringe and canular techniques)
- Flash Chromatography
- Synthetic techniques including
  - Oxidations (Swern, PDC, Dess-Martin, TPAP etc)
  - Reductions ( $\text{NaBH}_4$ ,  $\text{LiBH}_4$ , Raney nickel hydrazine etc)
  - Olefination chemistry
  - Mitsunobu chemistry
  - Nitrations
  - Protecting group chemistry
  - Palladium chemistry (especially Suzuki reactions)
- Combinatorial Chemistry (On solid support and in solution)
- Heterocyclic chemistry
- Solid Supported reagents and scavengers, catch and release techniques
- Microwave chemistry
- Automation (ACT396, IRORI and TRANSORT system)
- Interpreting NMR (1 and 2D), MS, IR etc

---

## Grants

CR-UK Programme Grant C180/A1060  
CR-UK Project Grant C180/A1066  
CR-UK Programme Grant C180/A5068  
CR-UK Studentship C180/A4522  
CR-UK Studentship C180/A2778  
EPSRC Case Award GR/PO1366/01  
CR-UK Equipment Grant C180/A3959

---

## Invited Lectures

SMi Drug Design, "Gene Targeting Approaches to Anti-Cancer Drug Design",  
London, UK (February 2003).

Societa Chimica Italiana Divisione Di Chimica Farmaceutica (Italian Medicinal  
Chemistry Summer School), Urbino, Italy (Jun-Jul 2003).

The Royal Society of Chemistry – Cancer Therapeutics in the 21st Century,  
Manchester, UK (October 2003).

25th Winter Meeting of the EORTC-PAMM Group, Bradford, UK (January  
2004).

Part 1 of SMi's Global Cancer Event - Innovations in Cancer Drug Discovery,  
"Design of Small Sequence-Selective DNA-Interactive Molecules", London,  
UK (June, 2004).

British Association of Cancer Research, Oxford, UK.

First European Conference on Chemistry for Life Sciences Rimini, Italy  
October 2005

---

## Hobbies and Outside Activities

Reading ancient and medieval history, amateur astronomy. I have also taken part in three "Relay for Life" fund raisers for CRC.

---

## Referees

### **Professor David Thurston**

Chief Scientific Officer, Spirogen Ltd  
The School of Pharmacy  
29-39 Brunswick Square  
London  
WC1N 1AX  
0207 753 5932/1  
E-mail [david.thurston@pharmacy.ac.uk](mailto:david.thurston@pharmacy.ac.uk)

### **Professor John Hartley**

Director of Research, Biology Spirogen Ltd  
UCL Cancer Institute  
Paul O'Gorman Building  
University College London  
72 Huntley Street  
London  
WC1E 6BT  
020 7679 6055  
E-mail [john.hartley@ucl.ac.uk](mailto:john.hartley@ucl.ac.uk)

### **Professor Malcolm Stevens**

CSO Pharminox  
Centre for Biomolecular Sciences  
University of Nottingham  
University Park  
Nottingham  
NG7 2RD  
Tel: 0115 951 3414  
E-mail: [malcolm.stevens@nottingham.ac.uk](mailto:malcolm.stevens@nottingham.ac.uk)

---

## Appendix

### Patents

Howard, Philip Wilson; Gregson, Stephen John; Taylor, Peter William; Thurston, David Edwin; Hadjivassileva, Tsveta Stepanova. **Preparation, DNA crosslinking reactivity, antitumor and antibacterial activity of pyrrolobenzodiazepine dimers.** PCT Int. Appl. (2005), 62 pp. CODEN: PIXXD2 WO 2005085260 A1 20050915 CAN 143:306350 AN 2005:1004755

Howard, Philip Wilson; Kang, Gyoung-Dong. **Preparation, DNA crosslinking reactivity and antiproliferative activity of pyrrolobenzodiazepine dimers.** PCT Int. Appl. (2005), 108 pp. CODEN: PIXXD2 WO 2005085259 A2 20050915 CAN 143:306349 AN 2005:1004754

Howard, Philip Wilson; Gregson, Stephen John. **Preparation of pyrrolobenzodiazepinone derivatives as antitumor agents.** PCT Int. Appl. (2005), 88 pp. CODEN: PIXXD2 WO 2005085251 A1 20050915 CAN 143:306348 AN 2005:1004748

Howard, Philip Wilson; Gregson, Stephen John; Tiberghien, Arnaud Charles. **Preparation of C8/C8' linked 5-oxo-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c]-1,4-benzodiazepine dimers with 1H-pyrrole-dicarboxylic acid amide linkers and oligomeric analogs thereof as well as related compounds for the treatment of proliferative diseases.** PCT Int. Appl. (2005), 108 pp. CODEN: PIXXD2 WO 2005085250 A1 20050915 CAN 143:306347 AN 2005:1004747

Howard, Philip Wilson; Wells, Geoffrey. **Preparation of aminobiaryl carboxylic acids for the manufacture of medicaments for treating proliferative disease.** PCT Int. Appl. (2005), 90 pp. CODEN: PIXXD2 WO 2005085177 A2 20050915 CAN 143:286420 AN 2005:1004692

Howard, Philip Wilson; Thurston, David Edwin; Gregson, Stephen John. **Preparation, DNA crosslinking reactivity and antitumor activity of pyrrolobenzodiazepines.** PCT Int. Appl. (2005), 24 pp. CODEN: PIXXD2 WO 2005042535 A1 20050512 CAN 142:463770 AN 2005:409522

Vishnuvajjala, B. Rao; Liu, Paul S.; Snader, Kenneth M.; Thurston, David; Howard, Philip W.; Turner, Gregory. **Method for preparation of pyrrolobenzodiazepine derivatives and compositions comprising them.** PCT Int. Appl. (2005), 89 pp. CODEN: PIXXD2 WO 2005040170 A2 20050506 CAN 142:447059 AN 2005:395315

Howard, Philip; Masterson, Luke. **Synthesis of protected pyrrolobenzodiazepines.** PCT Int. Appl. (2005), 120 pp. CODEN: PIXXD2 WO 2005023814 A1 20050317 CAN 142:316867 AN 2005:238991

Thurston, David Edwin; Howard, Philip Wilson. **Preparation of pyrrolobenzodiazepines as anticancer agents.** PCT Int. Appl. (2004), 74 pp. CODEN: PIXXD2 WO 2004043963 A1 20040527 CAN 140:423715 AN 2004:430806

Thurston, David Edwin; Howard, Philip Wilson. **Preparation of cyclopropylindole derivatives and peptide libraries containing them.** PCT Int. Appl. (2001), 69 pp. CODEN: PIXXD2 WO 2001016104 A1 20010308 CAN 134:208138 AN 2001:167967 CAPLUS

Thurston, David Edwin; Howard, Philip Wilson. **Solid-phase preparation and combinatorial libraries of pyrrolobenzodiazepine derivatives for drug screening.** PCT Int. Appl. (2000), 65 pp. CODEN: PIXXD2 WO 2000012509 A2 20000309 CAN 132:207852 AN 2000:161285

Thurston, David Edwin; Howard, Philip Wilson. **Preparation of pyrrolobenzodiazepines (PBDs) as antitumor agents.** PCT Int. Appl. (2000), 258 pp. CODEN: PIXXD2 WO 2000012508 A2 20000309 CAN 132:207851 AN 2000:161284

Thurston, David Edwin; Howard, Philip Wilson. **Preparation of pyrrolobenzodiazepines (PBDs) as antitumor antibiotics.** PCT Int. Appl. (2000), 101 pp. CODEN: PIXXD2 WO 2000012507 A2 20000309 CAN 132:207703 AN 2000:161283

Thurston, David Edwin; Howard, Philip Wilson. **Preparation of peptidyl pyrrolobenzodiazepines as pharmaceuticals.** PCT Int. Appl. (2000), 158 pp. CODEN: PIXXD2 WO 2000012506 A2 20000309 CAN 132:208134 AN 2000:161282

## **Publications**

. Minal Kotecha, Jerome Kluzza, Geoff Wells, C. Caroline O'Hare, Claudia Forni, Roberto Mantovani, Philip W. Howard, Peter Morris, David E. Thurston, John A. Hartley, and Daniel Hochhauser. **Inhibition of DNA binding of the NF- $\kappa$ B transcription factor by the pyrrolobenzodiazepine-polyamide conjugate GWL-78.** Mol. Cancer Ther. 2008 7: 1319-1328

Wells, Geoffrey; Suggett, Marie; Coffils, Marissa; Balg, Mirza A. H.; Howard, Philip W.; Loadman, Paul M.; Hartley, John A.; Jenkins, Terence C.; Thurston, David E. **Bioorganic & Medicinal Chemistry Letters** (2008), 18(6), 2147-2151 **Fluorescent 7-diethylaminocoumarin pyrrolobenzodiazepine conjugates: Synthesis, DNA interaction, cytotoxicity and differential cellular localization.**

Tiberghien, Arnaud C.; Evans, David A.; Kiakos, Konstantinos; Martin, Christopher R. H.; Hartley, John A.; Thurston, David E.; Howard, Philip W. **An asymmetric C8/C8'-tripyrrole-linked sequence-selective pyrrolo[2,1-c][1,4]benzodiazepine (PBD) dimer DNA interstrand cross-linking agent spanning 11 DNA base pairs.** Bioorganic & Medicinal Chemistry Letters (2008), 18(6), 2073-2077.

Narayanawamy, Mathangi; Griffiths, William J.; Howard, Philip W.; Thurston, David E. **An assay combining high-performance liquid chromatography and mass spectrometry to measure DNA interstrand cross-linking efficiency in oligonucleotides of varying sequences.** Analytical Biochemistry (2008), 374(1), 173-181.

Antonow, Dyeison; Cooper, Nectaroula; Howard, Philip W.; Thurston, David E. **Parallel Synthesis of a Novel C2-Aryl Pyrrolo[2,1-c][1,4]benzodiazepine (PBD) Library.** Journal of Combinatorial Chemistry (2007), 9(3), 437-445

Wells, Geoff; Martin, Christopher R. H.; Howard, Philip W.; Sands, Zara A.; Laughton, Charles A.; Tiberghien, Arnaud; Woo, Chi Kit; Masterson, Luke A.; Stephenson, Marissa J.; Hartley, John A.; Jenkins, Terence C.; Shnyder, Steven D.; Loadman, Paul M.; Waring, Michael J.; Thurston, David E. **Design, Synthesis, and Biophysical and Biological Evaluation of a Series of Pyrrolobenzodiazepine-Poly(N-methylpyrrole) Conjugates.** Journal of Medicinal Chemistry (2006), 49(18), 5442-5461.



Antonow, Dyeison; Jenkins, Terence C.; Howard, Philip W.; Thurston, David E. **Synthesis of a novel C2-aryl pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dione library: Effect of C2-aryl substitution on cytotoxicity and non-covalent DNA binding.** *Bioorganic & Medicinal Chemistry* (2007), 15(8), 3041-3053.

Masterson, Luke A.; Spanswick, Victoria J.; Hartley, John A.; Begent, Richard H.; Howard, Philip W.; Thurston, David E. **Synthesis and biological evaluation of novel pyrrolo[2,1-c][1,4]benzodiazepine prodrugs for use in antibody-directed enzyme prodrug therapy.** *Bioorganic & Medicinal Chemistry Letters* (2006), 16(2), 252-256.

Tiberghien, Arnaud C.; Hagan, David; Howard, Philip W.; Thurston, David E. **Application of the Stille coupling reaction to the synthesis of C2-substituted endo-exo unsaturated pyrrolo[2,1-c][1,4]benzodiazepines (PBDs).** *Bioorganic & Medicinal Chemistry Letters* (2004), 14(20), 5041-5044.

Alley, Michael C.; Hollingshead, Melinda G.; Pacula-Cox, Christine M.; Waud, William R.; Hartley, John A.; Howard, Philip W.; Gregson, Stephen J.; Thurston, David E.; Sausville, Edward A. **SJG-136 (NSC 694501), A Novel Rationally Designed DNA Minor Groove Interstrand Cross-Linking Agent with Potent and Broad Spectrum Antitumor Activity: Part 2: Efficacy Evaluations.** *Cancer Research* (2004), 64(18), 6700-6706.

Hartley, John A.; Spanswick, Victoria J.; Brooks, Natalie; Clingen, Peter H.; McHugh, Peter J.; Hochhauser, Daniel; Pedley, R. Barbara; Kelland, Lloyd R.; Alley, Michael C.; Schultz, Robert; Hollingshead, Melinda G.; Schweikart, Karen M.; Tomaszewski, Joseph E.; Sausville, Edward A.; Gregson, Stephen J.; Howard, Philip W.; Thurston, David E. **SJG-136 (NSC 694501), a Novel Rationally Designed DNA Minor Groove Interstrand Cross-Linking Agent with Potent and Broad Spectrum Antitumor Activity: Part 1: Cellular Pharmacology, In vitro and Initial In vivo Antitumor Activity.** *Cancer Research* (2004), 64(18), 6693-6699

Wilkinson, Gary P.; Taylor, James P.; Shnyder, Steve; Cooper, Patricia; Howard, Phil W.; Thurston, David E.; Jenkins, Terence C.; Loadman, Paul M. **Preliminary pharmacokinetic and bioanalytical studies of SJG-136 (NSC 694501), a sequence-selective pyrrolobenzodiazepine dimer DNA-cross-linking agent.** *Investigational New Drugs* (2004), 22(3), 231-240.

Chen, Zhizhi; Gregson, Stephen J.; Howard, Philip W.; Thurston, David E. **A novel approach to the synthesis of cytotoxic C2-C3 unsaturated pyrrolo[2,1-c]benzodiazepines (PBDs) with conjugated acrylyl C2-substituents.** *Bioorganic & Medicinal Chemistry Letters* (2004), 14(6), 1547-1549.

Masterson, Luke A.; Croker, Stephen J.; Jenkins, Terence C.; Howard, Philip W.; Thurston, David E. **Synthesis and biological evaluation of pyrrolo[2,1-c][1,4]benzodiazepine (PBD) C8 cyclic amine conjugates.** *Bioorganic & Medicinal Chemistry Letters* (2004), 14(4), 901-904.

Gregson, Stephen J.; Howard, Philip W.; Gullick, Darren R.; Hamaguchi, Anzu; Corcoran, Kathryn E.; Brooks, Natalie A.; Hartley, John A.; Jenkins, Terence C.; Patel, Sejal; Guille, Matthew J.; Thurston, David E. **Linker Length Modulates DNA Cross-Linking Reactivity and Cytotoxic Potency of C8/C8' Ether-Linked C2-exo-Unsaturated Pyrrolo[2,1-c][1,4]benzodiazepine (PBD) Dimers.** *Journal of Medicinal Chemistry* (2004), 47(5), 1161-1174.

Hardy, Alison; Berry, Jane M.; Brooks-Turner, Natalie; Howard, Philip W.; Hartley, John A.; Thurston, David E. **The generation and DNA-interaction of PBD and CBI libraries.** *Small Molecule DNA and RNA Binders* (2003), 2 697-710.

Kang, Gyoung-Dong; Howard, Philip W.; Thurston, David E. **Synthesis of a novel C2-aryl substituted 1,2-unsaturated pyrrolobenzodiazepine.** Chemical Communications (Cambridge, United Kingdom) (2003), (14), 1688-1689.

Gregson, Stephen J.; Howard, Philip W.; Thurston, David E. **Synthesis of the first examples of A-C8/C-C2 amide-linked pyrrolo[2,1-c][1,4]benzodiazepine dimers.** Bioorganic & Medicinal Chemistry Letters (2003), 13(14), 2277-2280.

Cooper, Nectaroula; Hagan, David R.; Tiberghien, Arnaud; Ademefun, Temitope; Matthews, Charles S.; Howard, Philip W.; Thurston, David E. **Synthesis of novel C2-aryl pyrrolobenzodiazepines (PBDs) as potential antitumor agents.** Chemical Communications (Cambridge, United Kingdom) (2002), (16), 1764-1765.

Berry, Jane M.; Howard, Philip W.; Kelland, Lloyd R.; Thurston, David E. **Synthesis and biological evaluation of an N10-Psec substituted pyrrolo[2,1-c][1,4]benzodiazepine prodrug.** Bioorganic & Medicinal Chemistry Letters (2002), 12(10), 1413-1416.

Gregson, S. J.; Howard, P. W.; Corcoran, K. E.; Jenkins, T. C.; Kelland, L. R.; Thurston, D. E. **Synthesis of the first example of a C2-C3/C2'-C3'-endo unsaturated pyrrolo[2,1-c][1,4]benzodiazepine dimer.** Bioorganic & Medicinal Chemistry Letters (2001), 11(21), 2859-2862.

Gregson, Stephen J.; Howard, Philip W.; Hartley, John A.; Brooks, Natalie A.; Adams, Lesley J.; Jenkins, Terence C.; Kelland, Lloyd R.; Thurston, David E. **Design, synthesis, and evaluation of a novel pyrrolobenzodiazepine DNA-interactive agent with highly efficient cross-linking ability and potent cytotoxicity.** Journal of Medicinal Chemistry (2001), 44(5), 737-748.

Sagnou, M. J.; Howard, P. W.; Gregson, S. J.; Eno-Amooquaye, E.; Burke, P. J.; Thurston, D. E. **Design and synthesis of novel pyrrolobenzodiazepine (PBD) prodrugs for ADEPT and GDEPT.** Bioorganic & Medicinal Chemistry Letters (2000), 10(18), 2083-2086.

Gregson, S. J.; Howard, P. W.; Barcella, S.; Nakamya, A.; Jenkins, T. C.; Kelland, L. R.; Thurston, D. E. **Effect of C2/C3-endo unsaturation on the cytotoxicity and DNA-binding reactivity of pyrrolo[2,1-c][1,4]benzodiazepines.** Bioorganic & Medicinal Chemistry Letters (2000), 10(16), 1849-1851.

Gregson, Stephen J.; Howard, Philip W.; Corcoran, Kathryn E.; Barcella, Simona; Yasin, Maqsood M.; Hurst, Abigail A.; Jenkins, Terence C.; Kelland, Lloyd R.; Thurston, David E. **Effect of C2-exo unsaturation on the cytotoxicity and DNA-binding reactivity of pyrrolo[2,1-c][1,4]benzodiazepines.** Bioorganic & Medicinal Chemistry Letters (2000), 10(16), 1845-1847.

Berry, J. M.; Howard, P. W.; Thurston, D. E. **Solid-phase synthesis of DNA-interactive pyrrolo[2,1-c][1,4]benzodiazepines.** Tetrahedron Letters (2000), 41(32), 6171-6174.

Baraldi, Pier Giovanni; Balboni, Gianfranco; Cacciari, Barbara; Guiotto, Andrea; Manfredini, Stefano; Romagnoli, Romeo; Spalluto, Giampiero; Thurston, David E.; Howard, Philip W.; Bianchi, Nicoletta; Rutigliano, Cristina; Mischiati, Carlo; Gambari, Roberto. **Synthesis, in Vitro Antiproliferative Activity, and DNA-Binding Properties of Hybrid Molecules Containing Pyrrolo[2,1-c][1,4]benzodiazepine and Minor-Groove-Binding Oligopyrrole Carriers.** Journal of Medicinal Chemistry (1999), 42(25), 5131-5141.

Wilson, Stuart C.; Howard, Philip W.; Forrow, Stephen M.; Hartley, John A.; Adams, Lesley J.; Jenkins, Terence C.; Kelland, Lloyd R.; Thurston, David E. **Design, Synthesis, and Evaluation of a Novel Sequence-Selective Epoxide-Containing DNA Cross-Linking Agent Based on the Pyrrolo[2,1-c][1,4]benzodiazepine System.** Journal of Medicinal Chemistry (1999), 42(20), 4028-4041.

Thurston, David E.; Bose, D. Subhas; Howard, Philip W.; Jenkins, Terence C.; Leoni, Alberto; Baraldi, Pier G.; Guiotto, Andrea; Cacciari, Barbara; Kelland, Lloyd R.; Foloppe, Marie-Paule; Rault, Sylvain. **Effect of A-ring modifications on the DNA-binding behavior and cytotoxicity of pyrrolo[2,1-c][1,4]benzodiazepines.** *Journal of Medicinal Chemistry* (1999), 42(11), 1951-1964.

Gregson, Stephen J.; Howard, Philip W.; Thurston, David E.; Jenkins, Terence C.; Kelland, Lloyd R. **Synthesis of a novel C2/C2'-exo unsaturated pyrrolobenzodiazepine cross-linking agent with remarkable DNA binding affinity and cytotoxicity.** *Chemical Communications (Cambridge)* (1999), (9), 797-798.

Baraldi, Pier Giovanni; Cacciari, Barbara; Guiotto, Andrea; Leoni, Alberto; Romagnoli, Romeo; Spalluto, Giampiero; Mongelli, Nicola; Howard, Philip W.; Thurston, David E.; Bianchi, Nicoletta; Gambari, Roberto. **Design, synthesis and biological activity of a pyrrolo[2,1-c][1,4]benzodiazepine (PBD)-distamycin hybrid.** *Bioorganic & Medicinal Chemistry Letters* (1998), 8(21), 3019-3024.

Guiotto, Andrea; Howard, Philip W.; Baraldi, Pier Giovanni; Thurston, David E. **Synthesis of novel C7-aryl substituted pyrrolo[2,1-c][1,4]benzodiazepines (PBDs) via pro-N10-Troc protection and Suzuki coupling.** *Bioorganic & Medicinal Chemistry Letters* (1998), 8(21), 3017-3018.

Kamal, Ahmed; Howard, Philip W.; Reddy, B. S. Narayan; Reddy, B. S. Praveen; Thurston, David E. **Synthesis of pyrrolo[2,1-c][1,4]benzodiazepine antibiotics: oxidation of cyclic secondary amine with TPAP.** *Tetrahedron* (1997), 53(9), 3223-3230.

Thurston, David E.; Bose, D. Subhas; Thompson, Andrew S.; Howard, Philip W.; Leoni, Alberto; Croker, Stephen J.; Jenkins, Terence C.; Neidle, Steven; Hartley, John A.; Hurley, Laurence H. **Synthesis of Sequence-Selective C8-Linked Pyrrolo[2,1-c][1,4]benzodiazepine Interstrand DNA Crosslinking Agents.** *Journal of Organic Chemistry* (1996), 61(23), 8141-8147

Howell, James A. S.; Bell, Andrew G.; O'Leary, Paula J.; Stephenson, G. Richard; Hastings, Michelle; Howard, Philip W.; Owen, David A.; Whitehead, Andrew J.; McArdle, Patrick; Cunningham, Desmond. **Synthesis and Reactivity of Cyclic and Acyclic [(1-(acyloxy)cyclopentadienyl)Fe(CO)2L]X and [(1-alkoxypentadienyl)Fe(CO)2L]X Salts (L = CO, PPh3).** *Organometallics* (1996), 15(20), 4247-4257.

Zioga, G.; Howard, P. W.; Canfield, L. M.; Gescher, A.; Thurston, D. E. **Interaction of the pyrrolobenzodiazepine antitumor agent anthramycin with glutathione: a possible role in metabolism.** *Pharmaceutical Sciences* (1996), 2(1), 39-42.

Wilson, Stuart C.; Howard, Philip W.; Thurston, David E. **Design and synthesis of a novel epoxide-containing pyrrolo[2,1-c][1,4]benzodiazepine (PBD) via a new cyclization procedure.** *Electronic Conference on Trends in Organic Chemistry [CD-ROM]* (1996), Meeting Date 1995, Paper 32.

Wilson, Stuart C.; Howard, Philip W.; Thurston, David E. **Design and synthesis of a novel epoxide-containing pyrrolo[2,1-c][1,4]benzodiazepine (PBD) via a new cyclization procedure.** *Tetrahedron Letters* (1995), 36(35), 6333-6.

Stephenson, G. Richard; Howard, Philip W.. **Circular dichroism spectra of tricarbonyliron  $\pi$ -complexes.** *Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999)* (1994), (19), 2873-80.

Howard, Philip Wilson. **The preparation and chemistry of dihydrocatechol derived organoiron complexes.** (1991), 280 pp.

Stephenson, G. Richard; Astley, Stephen T.; Palotai, Ian M.; Howard, Philip W.; Owen, David A.; Williams, Sarah. **Regiocontrolled applications of transition metal  $\pi$ -complexes.** Org. Synth. Organomet., Proc. Symp., 3rd (1991), Meeting Date 1990, 169-85.

Stephenson, G. Richard; Howard, Philip W.; Taylor, Stephen C. **Regioselective access to tricarbonyliron complexes: controlled preparation and reactions of trifluoromethyl substituted complexes.** Journal of Organometallic Chemistry (1991), 419(1-2), C14-C17

Stephenson, G. Richard; Howard, Philip W.; Owen, David A.; Whitehead, Andrew J. **Complementary regioselection in nucleophile additions to cationic  $\eta$  5-cyclohexadienyliron complexes.** Journal of the Chemical Society, Chemical Communications (1991), (9), 641-2.

Stephenson, G. Richard; Howard, Philip W.; Taylor, Stephen C. **Assignment of absolute configurations from the circular dichroism spectra of cyclic  $\eta$  4-diene complexes of iron tricarbonyl.** Journal of the Chemical Society, Chemical Communications (1991), (2), 127-9.

Howard, Philip W.; Stephenson, G. Richard; Taylor, Stephen C. **Evidence for an anomalous microbial oxidation of acetophenone: new access to optically active tricarbonyliron complexes.** Journal of the Chemical Society, Chemical Communications (1990), (17), 1182-4.

Howard, Philip W.; Stephenson, G. Richard; Taylor, Stephen C. **Transition metal mediated asymmetric synthesis. X. Homochiral  $\pi$ -complexes with planar chirality: synthetic equivalents of chiral cyclohexadiene dications.** Journal of Organometallic Chemistry (1989), 370(1-3), 97-109.

Howard, Philip W.; Stephenson, G. Richard; Taylor, Stephen C. **Convenient access to homochiral tricarbonyliron complexes.** Journal of the Chemical Society, Chemical Communications (1988), (24), 1603-4.

Stephenson, G. R.; Alexander, R. P.; Morley, C.; Howard, P. W..  **$\pi$ -Complexes with planar chirality: control centers for stereoselective synthesis.** Philosophical Transactions of the Royal Society of London, Series A: Mathematical, Physical and Engineering Sciences (1988), 326(1592), 545-56.

Howard, Philip W.; Stephenson, G. Richard; Taylor, Stephen C. **Transition metal mediated asymmetric synthesis. VII. 6-Methoxycyclohexadienyliron complexes: access to synthetic equivalents of cyclohexadiene dications.** Journal of Organometallic Chemistry (1988), 339(3), C5-C8.